urinary metabolites following ingestion of large amounts of Stilton and Camembert. This may have given rise to a popular misconception that cheeses with obvious visible and olfactory evidence of putrefaction necessarily contain most tyramine.

The amount of tyramine in individual samples of the same type of cheese shows variations which are often as wide as those between different cheeses. For instance, although Asatoor et al. estimated the tyramine content in one sample of Camembert cheese to be 2 mg. per g. other workers have found very little tyramine in cheeses of similar type (Kosikowsky and Dahlberg 1954, Simonart and Mayandon 1952). Almost all the clinical reports of hypertensive crisis incriminate Cheddar cheese which has frequently been shown to contain large amounts of tyramine (Silverman and Kosikowsky 1956). In one sample of Cheddar cheese (Bullock and Irvine 1956) the amount of tyramine (3·7 mg. per g.) was almost double that of Asatoor et al. for Camembert. Two cheeses (no. 6 and 8) known to have provoked hypertension both had high tyramine content, but the appearance was desiccated and unappetising; hence one patient was ashamed to admit eating the cheese and attempted to conceal it. Flavour is also an inaccurate indicator of tyramine content. The cause of flavour in Cheddar cheese is complex (Mabbitt 1961) and is not directly related to any single constituent, although lengthy maturation might increase flavour-producing substances coincidentally with tyramine. In this study a " mild " English Cheddar cheese (no. 3) contained more tyramine than a strong " mature " cheese (no. 7).

Individual Tyramine Content

An interesting feature of the hypertensive crisis has been the large number of patients taking amine-oxidase inhibitors who eat cheese with apparent impunity. At least one factor now seems to be the extreme variability in cheese composition; the tyramine content of 14 Cheddar cheeses ranged from 72 to 953 *u*g. per g. cheese. Horwitz et al. (1964) have shown that the blood-pressure effects of intravenous tyramine can be potentiated a hundredfold after amine-oxidase inhibition. As little as 6 mg. orally can raise the blood-pressure, although large rises may cause no subjective sensation and the amount required to induce a hypertensive crisis is probably in excess of this figure. Assuming an average portion of cheese to be about 50 g. (about 2 oz.) and 25 mg. to be a dangerous dose of tyramine, 4 cheeses in this series approach this figure (no. 6, 8, 10, 11) and 2 (no. 6, 8) are known to have provoked hypertension. The two patients were taking phenelzine (no. 6) and tranylcypromine (no. 8) for depression. The other patient (no. 7) was treated for hypertension with pargyline. In this case no tyramine could be detected in the cheese by the chromatographic method, but the patient had eaten a quantity of yeast extract (' Marmite ') at the same time, and this is also known to provoke hypertension (Blackwell et al. 1964).

Summary

A method for the quantitative estimation of amines in cheese was used to measure the tyramine content of several varieties of cheese, including three samples thought to have provoked a hypertensive crisis. Tyramine content is related to maturation-time, bacterial flora, and details of manufacture, but not necessarily to appearance or flavour. Cheddar cheese often contains sufficient tyramine to provoke hypertension, but individual samples differ widely in tyramine content, thus providing one explanation for the observation that many patients eat cheese with impunity, despite treatment with monoamine-oxidase inhibitors.

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Preliminary Communications

EFFECTS OF YEAST EXTRACT AFTER MONOAMINE-OXIDASE INHIBITION

INTERACTIONS between monoamine-oxidase inhibitors, other drugs, and food substances are now well recognised. Cheese remains the commonest dietary factor incriminated, but hypertensive crises were reported in 2 patients on a monoamine-oxidase inhibitor who had eaten broad beans,[1 2] and we have seen 2 patients with attacks of hypertension and severe headache after eating the yeast extract, ' Marmite '.[3 4] In cheese, tyramine is considered to be responsible [5–8] and in broad beans the aminoacid dopa or its amine derivative, dopamine, has been incriminated.[2] The causal agent in yeast extracts has not so far been identified.

Yeast extracts are manufactured by autolysing brewers' yeast cells in saline solution and allowing them to ferment for several hours. The product contains large numbers of peptides and aminoacids, but its exact composition, and in particular the concentration of amines, is uncertain. Chromatography of one yeast preparation (marmite) gave a tyramine-hydrochloride content of 1·5 mg. per g. Horwitz et al.[8] reported that as little as 6 mg. of tyramine hydrochloride was sufficient to produce hypertension in man after monoamine-oxidase inhibition. In 1 patient treated with an amine-oxidase inhibitor we found that 4 g. marmite (about half a teaspoonful, containing, according to our calculations, about 6 mg. tyramine hydrochlorite) raised the blood-pressure by 90 mm. Hg (fig. 1). In further experiments, the effects of yeast extract on the blood-pressure of the same patient under controlled conditions were very variable, suggesting the presence of

1. Blomley, D. *Lancet*, 1964, ii, 1181.
2. Hodge, J. V., Nye, E. R., Emerson, G. W. *ibid.* 1964, i, 1108.
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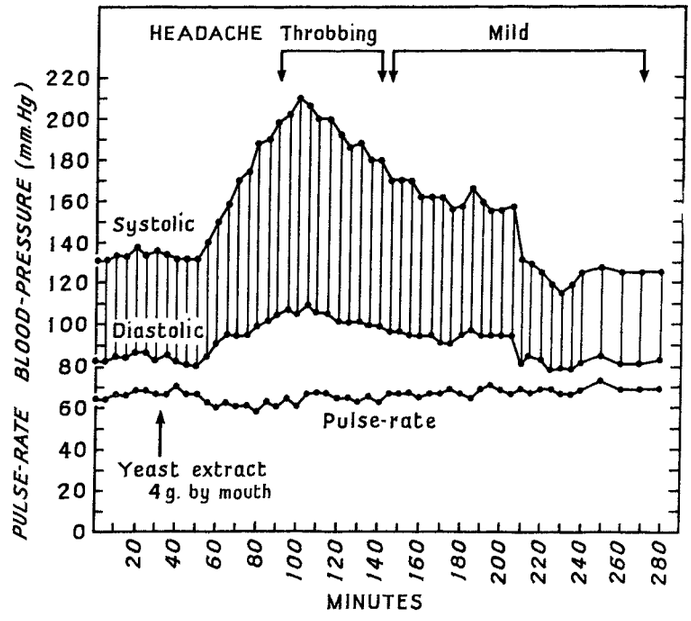

Fig. 1—Blood-pressure and pulse-rate changes after taking yeast extract (4 g.) orally preceded by tranylcypromine ('Parnate' 20 mg. orally) two hours earlier in a female patient treated for two years with tranylcypromine.

other substances besides tyramine. To elucidate this matter tests were made in animals.

LABORATORY EXPERIMENTS

The methods of anæsthetising and preparing animals for injecting drugs or foodstuffs into the duodenum or intravenously and for recording blood-pressure and tone of the nictitating membrane have been described previously.[7] For intravenous injection or for tests on the isolated guineapig-ileum, the yeast extract was first dissolved in saline solution and centrifuged to remove particles. The amine-oxidase inhibitor generally used was α-methylbenzyl hydrazine, since it has little sympathomimetic activity (which would have interfered with the results).

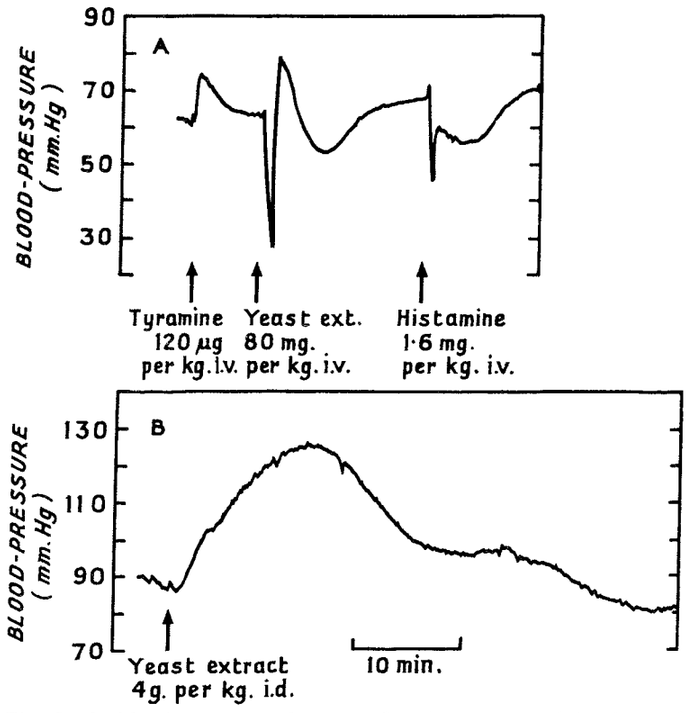

Fig. 2—A, blood-pressure changes after intravenous injections of tyramine, yeast extract and histamine in an untreated pithed rat. (Doses of drugs in all tracings given as the salt.) B, blood-pressure rise after intraduodenal administration of yeast extract in a pithed rat pre-treated with two intraperitoneal doses of α-methylbenzyl hydrazine (first dose 5 mg. per kg. twenty-four hours previously; second dose 5 mg. per kg. ninety minutes previously).

The effects of the yeast extract were also elicited with tranylcypromine and nialamide, the other amine-oxidase inhibitors tested. The isolated guineapig-ileum was suspended in a 20 ml. bath containing Krebs solution at 37°C gassed with 95% oxygen and 5% carbon dioxide. Contractions were recorded with a pendulum lever.[9]

RESULTS

The effects of marmite on the blood-pressure of the rat or cat could not be solely attributed to the presence of tyramine; it became apparent that a histamine-like substance was also present. The effects depended on the sensitivity of the preparation to the two amines.

Rat

Yeast extract injected intravenously into a pithed rat produced a rise in blood-pressure which was preceded and followed by a fall (fig. 2A). The response differed from that obtained with tyramine or histamine alone but could have been due to a combination of these substances. Yeast extract placed in the duodenum of a pithed rat had no effect on blood-pressure. But, when marmite was given intraduodenally after pretreatment with α-methylbenzyl hydrazine, the blood-pressure rose steeply (fig. 2B). This preponderance of the pressor effect was presumably due not only to potentiation of tyramine after monoamine-oxidase inhibition, but to the extreme sensitivity of the pithed rat to pressor substances and its relative insensitivity to histamine-like compounds.

Cat

Intravenous injection of histamine, marmite, or tyramine contracted the nictitating membrane (fig. 3A). Histamine and the yeast extract had depressor activity, but tyramine was pressor. The fall of blood-pressure with the yeast extract was generally followed by a rise in blood-pressure, although this is not shown in the figure. Marmite contains many organic bases which could liberate endogenous histamine. The depressor response with histamine release, however, is delayed in onset [10] and unlike the immediate fall in blood-pressure with histamine or yeast extract.

Marmite placed in the duodenum of the untreated cat

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10. MacIntosh, F. C., Paton, W. D. M. *ibid.* 1949, **109**, 190.

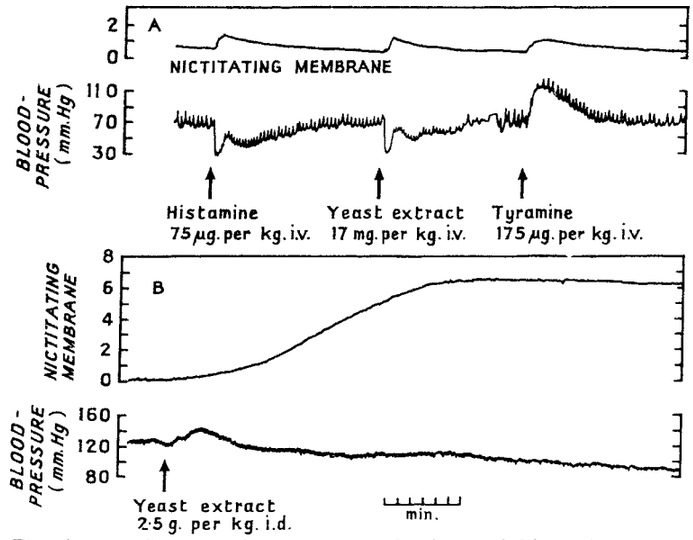

Fig. 3—A, effects of intravenous injections of histamine, yeast extract, and tyramine on the nictitating membrane and blood-pressure in an untreated cat anæsthetised with chloralose. B, sustained contraction of the nictitating membrane and fall of blood-pressure after intraduodenal administration of yeast extract in a cat anæsthetised with chloralose and given α-methylbenzyl hydrazine (20 mg. per kg. intraduodenally) ninety minutes previously.

was without effect on the blood-pressure or the nictitating membrane. But after pre-treatment with α-methylbenzyl hydrazine, marmite given intraduodenally produced long-lasting contraction of the nictitating membrane and a fall in blood-pressure. Less often, instead of the fall there was a small sustained rise in blood-pressure. The contraction of the nictitating membrane after intraduodenal yeast extract could be attributed to the combined effects of absorbed tyramine and histamine, whereas the effect on the blood-pressure was the resultant of the opposing actions of these amines. Because the chloralosed cat is sensitive to histamine, depressor responses were commoner.

Many other histamine-like effects of yeast extract were demonstrable in the chloralosed cat. These included an increase in limb volume, a rise in hæmatocrit, and increased volume of gastric secretion with the appearance of and subsequent increase in free-acid concentration. In addition, some of the effects of histamine were prolonged after amine-oxidase inhibition.

Other Tests for Histamine Activity

The presence of histamine in marmite was confirmed by special methods:

(1) As shown in fig. 4, the isolated guineapig-ileum in the presence of hyoscine contracts to histamine and to marmite. These contractions were abolished by the same concentration of a histamine antagonist, mepyramine. Antagonism was surmountable to the same degree by proportionately larger doses of histamine or the yeast extract.

(2) Histamine injected intravenously constricts the tracheobronchial muscle in guineapigs [11]; this response was also obtained with histamine placed in the gut with and without pre-treatment with a monoamine-oxidase inhibitor. Bronchial constriction was also produced by marmite given intravenously or intraduodenally and the effects were antagonised by mepyramine.

(3) To confirm the absorption of a histamine-like substance from the gut and its presence in the bloodstream we used a method described by Vane.[12] A strip of guineapig-ileum was superfused by carotid blood in the extracorporeal circulation of a cat. The guineapig-ileum contracts to histamine-like substances in the blood and did so ten to twenty minutes after placing yeast extract or histamine in the intestine of control cats, but *immediately* in cats pretreated with α-methylbenzyl hydrazine (20 mg. per kg.). The contraction of the strip was abolished by mepyramine.

(4) Chromatography of marmite revealed the presence of tyramine, histamine, and a substance believed to be a histamine-polypeptide complex.

The results indicated that marmite contains the equivalents of about 1·5 mg. per g. tyramine hydrochloride and up to 2 mg. per g. histamine acid phosphate, although exact amounts vary between samples and with modifications in the method of manufacture. Thus, one teaspoonful (about 10 g.) would contain the equivalents of 15 mg. tyramine hydrochloride and 20 mg. histamine acid phosphate. In healthy man, physiological effects are produced by intravenous injection of about 25 mg. tyramine hydrochloride and 2 mg. histamine acid phosphate.

DISCUSSION

Drugs which inhibit monoamine oxidase have long been known to interfere also with histaminase [13] and the histamine methylating enzyme.[14] Many of the diamines [15] and histamine [16] are also substrates for monoamine oxidase; for these reasons the effects of histamine could be augmented after treatment with monoamine-oxidase inhibitors. There has been no clinical evidence to support this view, but our investigations in animals on the effects of yeast extract after monoamine-oxidase inhibitors suggest that this factor may be relevant in several ways.

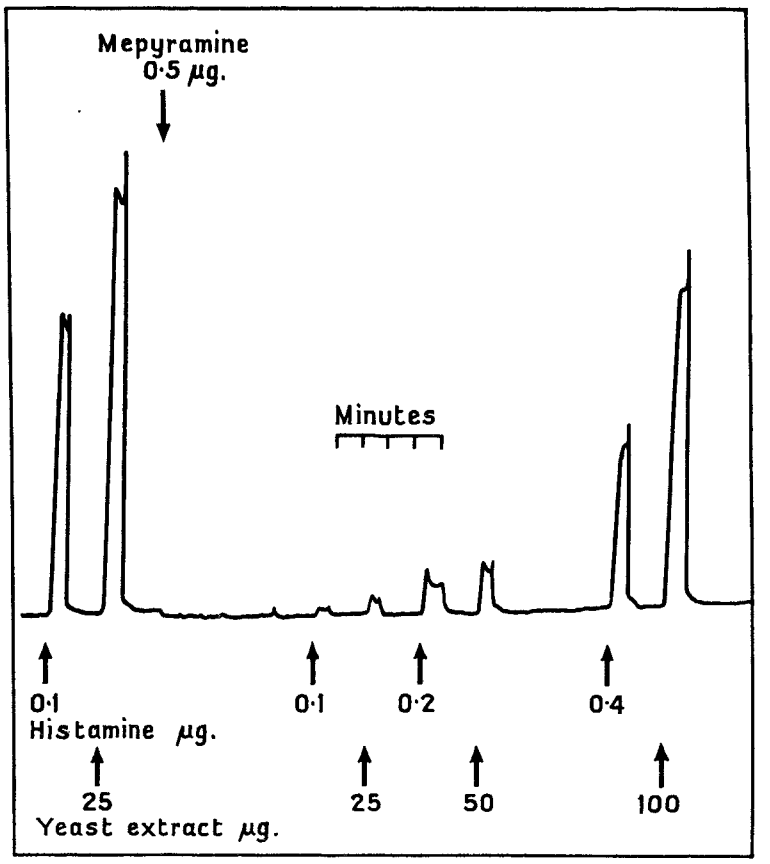

Fig. 4—Contraction of isolated guineapig-ileum by histamine and yeast extract in the presence of hyoscine (10^{-7}).

Contractions antagonised by mepyramine. Antagonism surmounted by larger doses of histamine and yeast extract. Doses represent final drug concentration in a 20 ml. bath.

Foods subjected in their preparation to putrefaction by micro-organisms which decarboxylate aminoacids will contain both monoamines and diamines. If tyrosine or histidine and their decarboxylases are present, then tyramine or histamine will be formed. In cheese, the conditions favour tyramine formation,[6] but histamine is occasionally formed,[17 18] and the aliphatic diamines, cadaverine and putrescine, are often present in larger amounts. In yeast extract conditions seem to favour the formation of histamine in relatively large quantities. The presence of histamine in foodstuffs and its enhanced absorption or potentiation after monoamine-oxidase inhibition in animals has not been previously demonstrated and may have several clinical implications.

Hypertensive Crises

The presence of tyramine in marmite could account for the hypertensive crises elicited in patients taking monoamine-oxidase inhibitors, but our observations, in patients on the effects of cheese or marmite on blood-pressure revealed a wide variation in response, despite standard conditions. Also, it is well known that many patients taking monoamine-oxidase inhibitors eat these foodstuffs with impunity. The variability of the blood-pressure effects was striking in animals and depended presumably on the relative quantities absorbed of the pressor and depressor amines, tyramine and histamine, and also on the sensitivity of the preparation to histamine. In man, the histamine absorbed from marmite would tend to counteract the rise in blood-pressure brought about by tyramine, but it must be borne in mind that histamine liberates cate-

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14. Schayer, R. W. *J. biol. Chem.* 1953, **203**, 787.
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17. Silverman, Kosikowsky, J. *J. Dairy Sci.* 1956 **39** :1134.
18. Block, R. J. *ibid.* 1951, **34**, 1.

cholamines from the adrenal medulla into the circulation and tyramine releases noradrenaline locally from sympathetic post-ganglionic nerve-endings. In this way they may potentiate one another if the concentration of catecholamines rises after long-continued monoamine-oxidase inhibition.

Hypotensive Collapse

Cooper [19] reported unexplained hypotensive collapse in patients taking α-methylbenzyl hydrazine. The possibility must be seriously considered that in such cases large quantities of histamine are absorbed from the gut after monoamine-oxidase inhibition or that endogenous histamine is liberated by drugs or food constituents not normally absorbed from the intestine.

Headache

In our patients the onset of headache was associated with the hypertension, although it sometimes persisted after the blood-pressure had returned to normal. The possibility arises that, independent of hypertension, some headaches may be caused or contributed to by histamine. Horwitz et al.[8] reported a case of headache and normal blood-pressure after the eating of cheese and Hodge et al.[2] recorded large rises in blood-pressure without headache.

Allergic Responses

We know of no reports of the precipitation or aggravation of allergic responses in susceptible patients taking monoamine-oxidase inhibitors. Because of the rapid absorption of histamine from the gut in some species after monoamine-oxidase inhibitors and the potentiation of the effects of histamine, this possibility should be considered by clinicians using the drugs.

SUMMARY

As a result of reports of adverse effects of yeast extracts in patients, the action of a yeast extract (' Marmite ') in animals was investigated. The extract contains tyramine and histamine, and there was evidence that the absorption of both substances from the intestine was facilitated and their actions potentiated after monoamine-oxidase inhibition. These findings may have clinical implications.

One of us (E. M.) gratefully acknowledges support from the Bethlem Royal and Maudsley Hospitals Research Fund. The other (B. B.) is supported by a grant from the Mental Health Research Fund.

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USE OF FREEZE-DRIED AORTIC VALVE HOMOGRAFTS IN AURAL SURGERY

I REPORT here the use of freeze-dried heart-valves in closing drum defects and for whole-drum replacement.

The valves are removed at necropsy, chemically sterilised, and then freeze-dried for storage. They are reconstituted by soaking in Ringer's solution before use. The tissue is elastic, easily handled, and strong and durable. There has been no evidence of rejection phenomenon or replacement.

In myringoplasty a portion of the valve is used to cover the outer surface of the drum remaining after the edges of the perforation have been freshened and the epithelial layer dissected back and retained in continuity with the meatal skin.

The epithelial layer is then repositioned to cover the graft as completely as possible and retained in place with foam-gel packs. The foam-gel is removed after three weeks when the graft is usually integrated with the epithelium, the canal healed, and the drum mobile.

Freeze-dried aortic-valve homografting has also been used successfully in complete-drum replacement after radical mastoidectomy. This was combined with cavity obliteration by the Guilford pedicled flap. Skin coverage of the graft was obtained by rotating a pedicled flap of meatal skin.

35 patients have been operated on in sixteen months. Of the first series of 21 cases, covering a year, 20 were completely successful technically. 1 failed to take owing to infection. In 2 cases the hearing was worse. 3 failed to report for follow-up audiometry, although adequate post-operative checks and microphotography were undertaken. 2 had ossicular discontinuity, and the operation was merely designed to seal off the middle ear in the first instance. In the remaining 13 cases there was notable improvement in hearing.

This technique seems to offer definite advantages over the standard methods using meatal skin, fascia, or vein autograft. But the series is small, and the longest follow-up is only sixteen months. It seems at this stage that aortic-valve homografts are of value particularly for the larger perforations and more extensive tympanoplastic procedures where failure of adequate revascularisation of autografts so commonly leads to immediate or delayed breakdown of the graft.

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Reviews of Books

Hernia

Editors: LLOYD M. NYHUS, M.D., F.A.C.S., professor of surgery, University of Washington School of Medicine, Seattle; HENRY N. HOSKINS, M.D., PH.D., F.A.C.S., professor and chairman of the department of surgery, University of Washington School of Medicine, Seattle. London: Pitman Medical Publishing Co. 1965. Pp. 836. 190*s*.

HOWEVER one defines a tome, this volume surely falls into the definition. Between them, 105 contributors from Europe (including Russia), the North American continent, and Asia expound their views on every conceivable aspect of groin, ventral, diaphragmatic, internal, and pelvic hernias. The general effect on the reader is a little like that of the television programme in which the tedium of a hackneyed subject is partly overcome by flying in distinguished guests from remote corners of the world to take part in the discussion. Yet the reader, even if he quails at the thought of wading through 836 pages on hernia, will nevertheless find much to interest him—the refreshing frankness of Mr. J. I. Hayward of Melbourne, for instance, who prefaces his comment on diaphragmatic hernia: " On this subject I am not sure of anything myself." Indeed, the whole section on diaphragmatic hernia is lively and well worth reading. Many recognised authorities deal with other forms of hernia—Lytle, McVay, Koontz, Tanner, Moloney, among others.

This is the book to end all books on hernia: surprisingly for a medical textbook, the writing is literate; each chapter is headed by an elegant and apt quotation, ranging from Proust to Shakespeare; the illustrations are lavish; and despite its size the book is reasonably easy to handle. Its price strengthens the suspicion that medical publishers are concentrating on medical libraries rather than individual buyers.